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Autologous Stem Cell Transplantation in Treatment of Aggressive Non-Hodgkin's Lymphoma

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There is no doubt that autologous stem cell transplantation is useful for patients with relapsed aggressive non-Hodgkin's lymphoma if they are responsive to the chemotherapy given before the transplantation. A small subset of patients with primary refractory disease still profits from this high dose chemotherapy regimen, but only if chemosensitive and if presenting with favorable risk factors at the moment of transplant eligibility. Autologous stem cell transplantation as upfront first line therapy for patients with aggressive non-Hodgkin's lymphoma does not contribute to a better outcome, most certainly not if it concerns patients with a favorable risk profile. There is still some doubt whether there is any place for autologous stem cell transplantation as first line therapy for patients with an unfavorable risk profile. Most randomized studies do not show an advantage, but more data are needed to definitely assess the place for this therapy option.

Key words: antineoplastic combined chemotherapy protocols; drug therapy; drug toxicity; lymphoma, non-Hodgkin's; transplantation, autologous; hematopoietic stem cell transplantation

Autologous stem cell transplantation is useful for patients with relapsed aggressive non-Hodgkin's lymphoma if they are responsive to the chemotherapy given before the transplantation. But for which category of patients with aggressive non-Hodgkin's lymphoma is autologous stem cell transplantation the best choice? The last two decades have shed more light on this difficult question. As high dose therapy was developed step-by-step, and always needs comparison with the so-called "gold" standard, some history is important.

Therapy through the Decades

Conventional Therapy in the 1960s and 1970s from First to Third Generation Chemotherapy

Patients with advanced aggressive non-Hodgkin's lymphoma can be effectively treated with multi-agent chemotherapy. Although the majority of patients below the age of 65 will reach a complete remission (CR) after CHOP-like (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, less than 50% will be finally cured (1). More intensive chemotherapy regimens, such as MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), ProMace-Cyta BOM (prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate, leucovorin, and septrin), or m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) generally yielded complete remission up to 80%, which is very high, but were apparently based upon data from highly selected patients with generally less unfavorable risk factors. Indeed, in a large randomized trial no difference was found between those three intensive chemotherapy regimens and classic CHOP (2).

Supra-high Dosed Chemotherapy:
 Autologous Stem Cell Transplantation

In the mid 1980s, high dose chemotherapy followed by autologous stem cell rescue became a mature therapy option, and appeared active for relapsing and refractory non-Hodgkin's lymphoma patients (3-6). Obviously, dose escalation could cure some patients with conventional chemotherapy-resistant disease. In the following years, patient selection became important to define which patients should be offered autologous stem cell transplantation. It appeared that the following selection criteria were important: a) autologous stem cell transplantation as second line treatment for truly relapsing patients vs primary refractory patients; b) early (upfront) transplantation for patients in their first line treatment vs transplantation for patients at relapse; and c) upfront autologous stem cell transplantation for patients with a favorable risk profile according to the International Prognostic Index (IPI) (7) vs an unfavorable IPI risk profile.

Autologous Stem Cell Transplantation for Patients in Relapse or Not Responding upon Initial CHOP-like Therapy.

Philip et al (8) performed a large randomized phase III trial, the PARMA trial, for patients with aggressive non-Hodgkin's lymphoma relapsing after a documented complete remission. He showed convincingly that autologous stem cell transplantation resulted in a better progression free survival and overall survival. It is important, however, to realize that many patients were excluded from this trial because of strict selection criteria, such as the absence of bone marrow infiltration or infiltration of the central nervous system during relapse. Ever since these results were published, autologous stem cell transplantation has been considered standard for patients below the age of 60-65 years, relapsing after CHOP-like chemotherapy.

Recently, Vose et al (9) showed that autologous stem cell transplantation could result in cure for a minority of patients who never achieved complete remission after induction chemotherapy. The most important factor for a successful outcome is whether a patient is still responsive to the second-line therapy and hence shows so-called chemosensitivity (10,11). Moreover, the age of the patient, the performance score, the lactate dehydrogenase (LDH) level, and stage of the disease, e.g., the IPI score at relapse, are

important criteria for the prediction if such a therapy is justified for this category of patients (12).

Randomized Phase III Studies Incorporating Autologous Stem Cell Transplantation as First Line Therapy

In large overviews covering more than 1,200 patients, Goldstone (13) and Armitage (14) compared the results from patients who underwent transplantation while in first complete remission, first partial remission, second complete remission, or during relapse/progressive disease. The analysis of these compiled data showed that this form of bone marrow ablative therapy could result in long-term disease-free survival in more than half of the patients receiving the transplant at a time of minimal disease (e.g., during first complete remission), early in the course of their lymphoma. However, selection might have played a major role in the outcome of these patients, because none of them had been treated in randomized phase III trials.

Therefore, aiming to improve the outcome in patients with aggressive non-Hodgkin's lymphoma, many groups initiated multicenter, phase III randomized trials comparing autologous stem cell transplantation with some form of standard chemotherapy for patients early in the phase of their disease. Most studies included patients aged 15-60 with a newly diagnosed stage II-IV aggressive non-Hodgkin's lympho-

Table 1. Overview of randomized trials with more than 100 patients incorporating early autologous stem cell transplantation for patients with aggressive non-Hodgkin's lymphoma^a

Protocol used by study group	No. of patients		IPI category: favorable/unfavorable	Full "standard" chemotherapy before transplantation	Consolidation regimen	Duration/follow-up (months)	Outcome
	enrolled/randomized	received transplant (%)					
HOVON 3, Verdonck et al (22)	286/69	76	all IPI	no; 4 CHOP	TBI/cyclo	36	no difference in OS and DFS for patients in PR after 3 CHOP
GELA LNH87-2, Haioun et al (23)	881/464	76	all IPI	yes; 6 CHOP-like	CVB	30	no difference in OS or DFS
GELA LNH87-2, with 2 or 3 risk factors (24)	451/236	69	unfavorable	idem	idem	96	high risk subset: ASCT arm superior for OS and DFS
Italian NHLCSG, Santini et al (25)	124/124	71	all IPI	yes; 12 weeks VACOP-B ^b	BEAM	42	no difference in OS, DFS or PFS; subset IPI HI and high: auto-SCT arm better DFS, but no difference in OS or PFS
Milan, single center, Gianni et al (26)	101/98	100	all IPI	no; sequential high dose ^c	TBI/Bu or mitox./Bu ^d	55	high dose better DFS, no difference in OS (P=0.09)
GELA LNH94-3, Gisselbrecht et al (11)	397/370	74	unfavorable	no; sequential high dose	BEAM or CVB	60	premature closure due to a high % failures and relapses
EORTC 20901, Kluin-Nelemans et al (27)	311/194	61	all IPI	yes; 6 CHOP-like	BEAC	53	no difference in OS or FFP
German High Grade Lymphoma Study Group, Kaiser et al (28)	312/262	67	all IPI	no; 3 CHOP-like	BEAM	12	no difference in OS, neither in the IPI unfavorable subset
BNLI/Nordisk/ Australasian Linch et al (29)	457/457	62	unfavorable	no; 3 CHOP	BEAM	54	no difference in OS; only IPI high and HI patients
GOELAM, Milpied et al (30)	207/197	81	all, except IPI high risk	no; 2 CEEP, HD MTX	BEAM	46	ASCT better EFS outcome. OS difference marginal. No IPI high risk patients included. Subset analysis of favorable group: no differences; of intermediate high IPI subset: EFS and OS better. Of note, at an earlier analysis in 1998, both arms were equal (31).

^aAbbreviations: IPI – International Prognostic Index; CHOP – cyclophosphamide, doxorubicin, vincristine, prednisolone; TBI – total body irradiation; OS – overall survival; DFS – disease free survival; PR – partial remission; LNH – lymphoma, non-Hodgkin; CVB – cyclophosphamide, etoposide (VP-16), BCNU (bischloroethyl nitrosourea, or carmustine); NHLCSG – non-Hodgkin's lymphoma cooperative study group; ASCT – autologous stem cell transplantation; VACOP-B – etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; DHAP – dexamethasone, cytarabine, cisplatin; CR – complete remission; BEAM – BCNU, etoposide, cytarabine, melphalan; PFS – progression-free survival; Bu – busulfan; EORTC – European Organization of Research and Treatment of Cancer; BEAC – BCNU, etoposide, cytarabine, and cyclophosphamide; BNLI – British National Lymphoma Investigation; GOELAM – Groupe Ouest Est Leucémies Aigues Myéloblastiques; FFP – free from progression; HI – high-intermediate; CEEP – cyclophosphamide, vindesine, etoposide, prednisone; HD MTX – high-dose methotrexate; EFS – event-free survival.

^bControl arm incorporated DHAP if no CR after VACOP-B.

^cCross-over was allowed.

^dTBI was replaced by mitoxantrone because of excessive toxicity.

ma. For elderly patients (≥ 65 years), high-dose chemotherapy was, and still is, considered too toxic.

A selected summary of published randomized trials incorporating autologous stem cell transplantation, and their data, we can conclude that thus far most studies have not shown the advantage of autologous stem cell transplantation over other forms of therapy in patients with aggressive non-Hodgkin's lymphoma belonging to the IPI low and intermediate-low risk categories (Table 1). There are no conclusive data for patients with an unfavorable risk profile (IPI high and intermediate-high), since different studies found different outcomes in such patients after autologous stem cell transplantation.

Statistics and Toxicity

Most studies have been designed to detect a 20% difference or more in time to progression over 5 years in favor of the autologous stem cell transplantation therapy. For most groups, this difference seemed justified, assuming that any smaller difference would not be clinically relevant in view of the expected toxicity of the autologous stem cell transplantation arm. A 20% difference would nowadays be considered too optimistic. Moreover, given the low autologous stem cell transplantation-related short-term toxicity, found in most studies (the combination of total body irradiation and busulfan excluded), smaller differences would also be of interest. Using very sophisticated methods, the French Groupe d'Etude des Lymphomes de l'Adulte (GELA group) additionally analyzed the quality of life of patients who had undergone autologous stem cell transplantation (15). They demonstrated that patients with transplants had more months without symptoms and toxicity than the control group. The advantage was more pronounced in high-risk patients (15). On the other hand, a Dutch evaluation on quality of life based upon low numbers of patients (6-13 per time point and per group) with the autologous stem cell transplantation arm showed that they had more complaints during the first 6 months, presumably due to the total body irradiation regimen (16).

Presently, it is important to look at long-term toxicity as well. New data demonstrate an alarmingly high incidence of secondary malignancies following autologous stem cell transplantation procedures (17-20). This should question the application of high-dose chemotherapy in non-Hodgkin's lymphoma patients if the chances of improvement are not substantial.

Subgroup Analysis According to Risk Profiles and Pathology

Patients with non-Hodgkin's lymphoma, so-called aggressive lymphoma (formerly designated as non-Hodgkin's lymphoma of intermediate and sometimes high malignancy grade), fall into all kinds of risk groups with highly different prognoses. Four risk groups can be identified by IPI (7), an international scoring model used at diagnosis for estimating the chance to attain complete remission of aggressive lymphoma by CHOP-like therapy. IPI is based on the following parameters at diagnosis: age, performance

status, LDH level, stage of the disease, and number of extranodal localizations. Moreover, pathology subgroups defined according to the World Health Organization's classification (21) also discriminate subgroups with large differences in overall survival and disease-free survival. Subset analyses on pathology subgroups have not been performed as yet. A meta-analysis will be needed to answer this question retrospectively. Moreover, the wish to incorporate anti-B cell monoclonal antibodies in new studies will specifically exclude patients with anaplastic large cell lymphoma or peripheral T cell lymphoma. It is clear that most groups will not be able to perform on their own phase III studies on subsets of patients with aggressive non-Hodgkin's lymphoma. Only large intergroup randomized studies will be statistically powerful enough to provide meaningful answers.

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